[CASE REPORT]

Generalized Eruptive Histiocytomas and Rosai-Dorfman Disease Presenting Concurrently in a Patient with Myelodysplastic Syndrome

[a]BENJAMIN KAFFENBERGER, MD; [a,b]KAMRUZ DARABI, MD; [b]SARA PETERS, MD; [c]JESSICA KYNYK, MD; MARK BECHTEL, MD

[a]Division of Dermatology, [b]Division of Dermatopathology, [c]Division of Pulmonary Medicine, Ohio State University College of Medicine, Columbus Ohio

ABSTRACT

Non-Langerhans cell histiocytoses were originally described as individual diagnoses. However, evidence has been mounting that these entities are manifestations on a spectrum of the same disease. The authors present a patient who initially presented with lymphadenopathy, pancytopenia, splenomegaly, and high-grade fevers. A bone marrow biopsy was performed and she was diagnosed with myelodysplastic syndrome with trisomy 8. Several months later, her persistent pulmonary lymphadenopathy was biopsied revealing Rosai-Dorfman disease. Two years after her initial hospitalization, the patient presented with lesions consistent with generalized eruptive histiocytomas. This case highlights the difficulty that clinicians encounter when trying to separate generalized eruptive histiocytomas, Rosai-Dorfman disease, and the other non-Langerhans cell histiocytoses. While further research needs to be performed in the field of histiocytoses, this case provides clinical support that these diseases are closely linked.
(*J Clin Aesthet Dermatol.* 2012;5(8):42–46.)

A 60-year-old Caucasian woman with a long history of unexplained lymphadenopathy was admitted to the hospital with worsening hilar lymphadenopathy, high-grade fevers, pancytopenia, and an absolute neutrophil count of 1500. Her erythrocyte sedimentation rate (ESR) was elevated at 76 and she had a notable γ-globulinopathy. A positron emission tomography/computed tomography (PET/CT) demonstrated increased metabolic activity in her bilateral femurs and tibias, widespread lymphadenopathy, and borderline hepatosplenomegaly. A bone marrow biopsy was performed and the patient was diagnosed with myelodysplastic syndrome (MDS), characterized as refractory cytopenia with multilineage dysplasia and ringed sideroblasts. Trisomy 8 was seen on chromosome analysis. An inguinal lymph node biopsy revealed sinus histiocytosis with positive S100 protein, and CD1a cell markers, the immunohistochemistry (IHC) of Langerhans cell histiocytosis (LCH). However, the sample lacked significant lymphocytic proliferation and eosinophils and these findings were felt to be secondary to the MDS. The patient defervesced without empiric antibiotics. Her cell counts recovered within the following week, except a persistent anemia. Her thrombocytopenia and leukopenia never recurred, and her anemia resolved after several months of darbepoetin treatment. She continued to follow with her pulmonologist for her abnormal chest CT, hilar lymphadenopathy, and patchy ground-glass opacities. Her disease progressed and due to clinical concern for sarcoidosis, connective tissue lung disease, or malignancy, she underwent mediastinoscopy. A lymph node resection of the right hilum showed sinus histiocytosis with positive S100 and CD68 expression and negative CD1a expression. Based on these findings, she was diagnosed with Rosai-Dorfman disease (RDD) six months after her hospitalization. A summary of the patient's pathology reports are shown in Table 1. Two years after being diagnosed with MDS and 1.5

DISCLOSURE: The authors report no relevant conflicts of interest.
ADDRESS CORRESPONDENCE TO: Benjamin H. Kaffenberger; E-mail: Benjamin.Kaffenberger@osumc.edu

TABLE 1. Biopsy results

DATE	LOCATION	BIOPSY TYPE	REASON	RESULTS
5/04	Left palm	Punch	Cyst	Spindled and histiocytoid dermal-based infiltrates of heterogeneous composition. Some have amphophilic quality of cytoplasm and many cells with finely vacuolated cytoplasms compatible with intracytoplasmic lipidization and scattered Touton Giant Cells. Suggestive of palmar xanthoma versus benign fibrous histiocytoma.
5/08	Bone marrow	Bone marrow	Pancytopenia, fevers	Hypercellular bone marrow (85%) with trilineage dysplasia and ringed sideroblasts. Scattered T and few B cells, predominantly single, plasma cells with focal small groups CD138+. Plasma cells are polyclonal. Clone of cells with trisomy 8 as sole abnormality.
5/08	Left inguinal node	Lymph node	Lymphadenopathy	Lymph node hyperplasia; sinus histiocytosis. Atypical paracortical histiocytic proliferation with increased Langerhans cells; CD3/CD20—highly organized immune architecture; CD 68—histiocytic cells, S100+, CD1a+. Consistent with Langerhans but lymphoid poor, no eosinophils. Resembles dermatopathic lymphadenitis but no pigment. Unlikely to be Langerhans with no lesional proliferation.
12/08	Transbronchial	Lymph node	Lymphadenopathy	Scattered S100+, CD1a-, CD68++. Flow cytometry—no abnormal B or T cell population mild elevation of CD4/CD8. Sinus histiocytosis, no evidence of lymphoma.
4/10	Right chest	Shave	Eruptive dermatofibroma exanthema, histiocytoma	Lesion of epithelioid cells and multinucleated cells surrounded by fibrosis. Occasional Touton-type giant cells present. S100-, CD1a-, CD68+, Factor XIIIA+, CD163+ Alpha-1 antitypsin-. HHF35-. Consistent with generalized eruptive histiocytomas

years after being diagnosed with RDD, the patient was seen in the university dermatology clinic for evaluation of scattered, noncoalescent flesh-colored and erythematous papules that had developed over the previous several months. The papules spread from her abdomen, superiorly to her thorax, neck, and across her upper extremity (Figure 1). The pathology under hematoxylin and eosin (H&E) staining and immunohistochemistry (IHC) is shown in Figure 2.

DISCUSSION

The patient in this case was diagnosed with RDD and, later, generalized eruptive histiocytomas (GEH), which are described as two separate non-Langerhans cell histiocytoses (nLCH) disorders. To the authors' knowledge, this is the first time that multiple nLCH disorders have coexisted. The patient initially exhibited hilar lymphadenopathy, sinus histiocytosis, and IHC consistent with RDD. Her γ-globulinopathy and elevated ESR also may be seen in RDD. While RDD can be cutaneous, the lesions present were not consistent based on negative S100 protein staining (Table 2). GEH is a rare histiocytic process limited to the dermis; it was originally described in three adults in 1963.[1] Table 2 contains six nLCH disorders that were considered in the differential diagnosis.

RDD and GEH are individually described entities within the histiocyte family. In these disorders, the underlying problem results from CD34+ myeloid progenitor cells and the numerous steps that are undertaken prior to presentation of disease in the skin, lymph nodes, or other internal organs.[2–3] An initial ordering system was suggested in 1987—class 1 includes LCH, class 2 includes nLCH, and class 3 includes malignant histiocytic disorders.[4] However, several inconsistencies exist. Indeterminate cell histiocytosis (ICH) appears to bridge the gap between LCH and nLCH. ICH has identical IHC as LCH and can only be differentiated ultrastructurally.[5–6] In addition, RDD and LCH have presented concurrently in multiple cases adding to developing arguments for a spectrum of class 1 and 2 disease.[7] Notably in this case, the patient's initial lymph node biopsy was CD1a and S100 protein positive, which is consistent with LCH, not RDD. However, morphologically it did not appear to be typical LCH. This further supports the argument that the coexistence of possible class 1 and class 2 disease may be more common than previously thought. Within class 2 or the nLCH family, there are many classic and even more rare syndromes. Classic nLCH variants include generalized eruptive histiocytomas (GEH), sinus

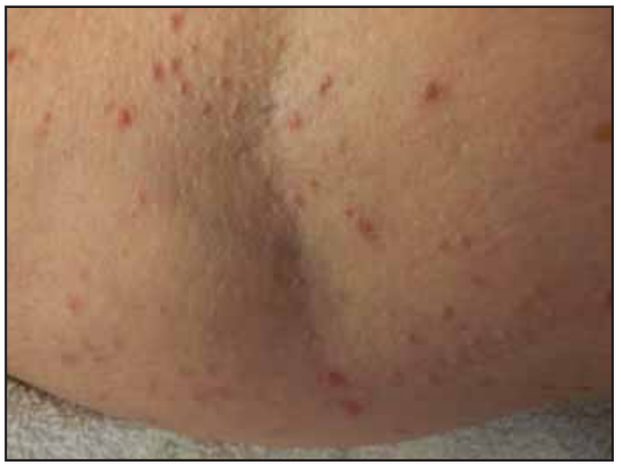

Figure 1. Dense, flesh-colored, erythematous, noncoalescing papules over the antecubital fossa

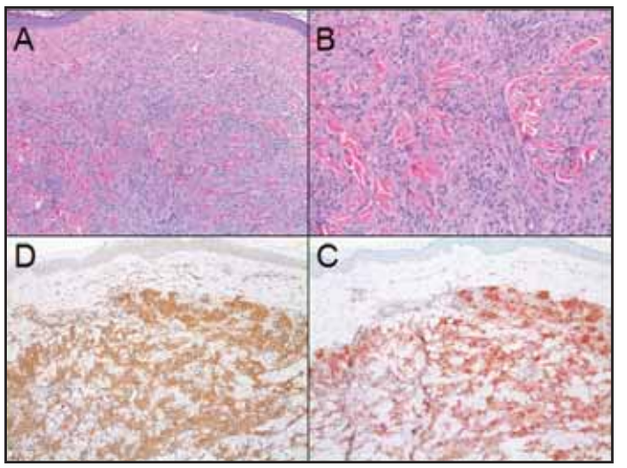

Figure 2. Histopathology of right upper chest lesion. Clockwise from top left. (A) H&E section at 100x demonstrating epithelioid cells and multinucleated epithelioid cells in a coarse collagen background with lesional cells extending to biopsy base. (B) H&E section 200x. (C) CD68 positive (red) for nearly all lesional cells in the dermis. (D) CD163 stain (brown) positive for nearly all cells in the dermis. Data not shown: S100 and CD1a negative with only internal positive control, Alpha-1-antitrypsin negative and HHF35 is negative, and Factor XIIIa faintly positive.

histiocytosis with massive lymphadenopathy or RDD, benign cephalic histiocytosis (BCH), xanthogranuloma (XG), papular xanthoma, xanthoma disseminatum (XD), and multicentric reticulohistiocytosis. While each entity was described separately, a consensus is developing that these nLCH disorders are a spectrum of one entity.[8–15] Members of the nLCH family can be difficult to distinguish due to the histopathological similarity of these entities. It is often impossible to render the histological diagnosis of multicentric reticulohistiocytosis, GEH, BCH, or XD without clinicopathological correlation.

Newer classification schemes attempt to prognosticate, stratifying based on maturity and thus the inverse correlation with the propensity to regress.[16] Another scheme suggests that all dermal nLCH disorders are along the spectrum of XG because XG contains all five morphological appearances of histiocytes.[17–18] A review hypothesized that a XG and non-XG spectrum may adequately classify noncutaneous disease as well.[19] Several case reports support this hypothesis after XG class disorders developed into another named disorder, including GEH developing into XD[20] and BCH morphing into XG in two other patients.[21–22] Interestingly in this case, RDD would be classified in the non-XG class that Weitzman extrapolated from Zelger, whereas GEH is in the XG class.[17–19] It is unclear how much the initial MDS impacted the development of the nLCH disorders in this case.

Research recently has shown CD34+ cells with trisomy 8 from patients with MDS are resistant to apoptosis.[23] These same CD34+ cells are accountable for histiocyte development. It is possible that the patient's clone of CD34+ with trisomy 8 provided an overload of stem cells that developed into different histiocyte proliferations. It is also unclear when she first developed this abnormal clone of myeloid progenitors. Even though her cell counts had recovered and were stable when diagnosed with RDD and GEH, the nodal and skin proliferations likely resulted from a common precursor, secondary to her MDS. This case appears to suggest that individual members within the nLCH family are closely related and may indeed be a spectrum of diseases. However, further research is needed in the field of histiocytoses. It also provides further association of nLCH disorders with myeloid dysplasia.

REFERENCES

1. Winkelmann RK, Muller SA. Generalized eruptive histiocytoma: a benign papular histiocytic reticulosis. *Arch Dermatol.* 1963;88:586–596.
2. Caux C, Dezutter-Dambuyant C, Schmitt D, et al. GM-CSF and TNF alpha cooperate in the generation of dendritic Langerhans cells. *Nature.* 1992;360:258–261.
3. Caux C, Vanbervliet B, Massacrier C, et al. CD34+ hematopoietic progenitors from human cord blood differentiate along two independent dentritic cell pathways in response to GM-CSF + TNFA. *J Exp Med.* 1996;184:695–706.
4. Chu A, D'Angio G, Favara D. Histiocytosis syndromes in children. *Lancet.* 1987:1:208–209.
5. Favara B, Feller A, WHO Committee Histiocytic/Reticulum Cell Proliferations: Pauli M, et al. Contemporary classification of histiocytic disorders. *Med Pediatr Oncol.* 1997;29:157–166.

TABLE 2. Review of pertinent differentials within nLCH

	INDETERMINATE CELL HISTIOCYTOSIS	GENERALIZED ERUPTIVE HISTIOCYTOMAS	BENIGN CEPHALIC HISTIOCYTOSIS	XANTHOMA DISSEMINATUM	ROSAI-DORFMAN DISEASE	SECONDARY HEMOPHAGOCYTIC LYMPHO-HISTIOCYTOSIS
AGE	Primarily adults although increasing numbers of children[6,14]	Primarily adults, growing body of child literature[24,25]	Infants and children[26]	All ages. Previously described as more common in those <25 years of age.[27] However, more recent review average age is 40.[28]	Mean age 20.6 with wide range[19]	In adults, mean age 56[29]
COLOR, DISTRIBUTION OF SKIN LESIONS	Papules or nodules, often solitary, varying hues of red and brown. Asymptomatic	Numerous flesh colored to red hued papules that may coalesce. Primarily trunk and extremities. Asymptomatic	Eruption papules, over face, cheeks, and eyelids. Fewer than generalized eruptive histiocytomas. Asymptomatic	Numerous flesh colored to reddish-brown papules symmetrically erupting over face, flexural, and intertriginous areas. Mucous membrane involvement. May coalesce. Asymptomatic	Red, red-brown macules, papules, nodules, or plaques, frequently in the eyelids or malar regions. Usually associated with lymphadenopathy. Rarely solely cutaneous	No specific eruption documented with syndrome
SYSTEMIC FINDINGS/ SEQUELLAE	Rare: myeloid cancers[30–32]	Rare: myeloid cancers[33–34]	Rare: insulin-dependent diabetes mellitus 7 years later,[35] diabetes insipidus (DI)[36]	Frequent: DI in 40%[28] Rare: monoclonal gammopathies, multiple myeloma,[37] neurologic demise,[38] upper airway obstruction[39]	Cervical lymphadenopathy, fevers, hypergamma-globulinemia	Fever, pancytopenia, splenomegaly, hepatitis
IHC **S100** **CD1A** **CD 68** **XIIIA** **BBG**	 Positive Positive Positive Positive Negative	 Negative Positive/Negative Positive Positive Negative	 Negative Positive Positive Positive Negative	 Negative Negative Positive Positive Negative	 Positive Negative Positive Positive Negative	
COURSE	If single, is usually removed, however if multiple, the course is generally indolent,[6] small subset have progressed to more malignant course[6,14]	At least partial resolution in 13/17 patients with follow-up[24]	Resolves on its own completely in a mean 50 months[26]	Most commonly stable muco-cutaneous disease without regression.[28] Less commonly resolves and rarely is progressive	82% of untreated patients had complete regression[40]	Mortality rate in one series 72%[29]

6. Caputo R, Marzano A, Passoni E, et al. Unusual variants of non-Langerhans cell histiocytoses. *J Am Acad Dermatol.* 2007;57:1031–1045.
7. Malley D, Duong A, Barry T, et al. Co-occurence of Langerhans cell histiocytosis and Rosa-Dorfman disease: possible relationship of two histiocytic disorders in rare cases. *Mod Pathol.* 2010:12:1616–1623.
8. Caputo R, Ermacora E, Gelmetti C, et al. Generalized eruptive histiocytoma in children. J Am Acad Dermatol. 1987;17:449–454.
9. Umbert IJ, Winkelmann RK. Eruptive histiocytoma. *J Am Acad Dermatol.* 1989;10:958–964.
10. Gianotti R, Alessi E, Caputo R. Benign cephalic histiocytosis: a distinct entity or a part of a wide spectrum of histiocytic proliferative disorders of children. *Am J Dermatopathol.* 1993;15:315–319.
11. Goerdt S, Bonsmann G, Sunderkotter C, et al. A unique non-Langerhans cell histiocytosis with some features of generalized eruptive histiocytoma. *J Am Acad Dermatol.* 1994;31:322–326.
12. Sidoroff A, Zelger B, Steiner H, et al. Indeterminate cell histiocytosis—a clinicopathological entity with features of both X-and non-X histiocytosis. *Br J Dermatol.* 1996;134:525–532.
13. Ferrando J, Campo-Voegelli A, Soler-Carillo J, et al. Systemic xanthohistiocytoma: a variant of xanthoma dissemenatum? *Br J Dermatol.* 1998:138:155–160.
14. Ratzinger G, Burgdorf W, Metze D, et al. Indeterminate cell histiocytosis: fact or fiction? *J Cutan Pathol.* 2005;32:552–560.
15. Sidwell RU, Francis N, Slater DN, et al. Is disseminated juvenile xanthogranulomatosis benign cephalic histiocytosis? *Pediatr Dermatol.* 2005;22:40.
16. Chu A. The confusing state of the histiocytoses. *Br J Dermatol.* 2000;143:475–476.
17. Zelger B, Sidoroff A, Orchard G, et al. Non-Langerhans cell histiocytoses. A new unifying concept. *Am J Dermatopathol.* 1996;18:490–504.
18. Zelger B, Cerio R. Xanthogranuloma is the archetype of non-Langerhans cell histiocytoses. *Br J Dermatol.* 2001;45:369–370.
19. Weitzman S Jaffe R. Uncommon histiocytic disorders: the non-Langerhans cell histiocytoses. *Pediatr Blood Cancer.* 2005;45:256–264.
20. Repiso T, Roca-Miralles M, Kanitakis J, et al. Generalized eruptive histiocytoma evolving into xanthoma disseminatum in a 4-year-old boy. *Br J Dermatol.* 1995;132:978–982.
21. Zelger BG, Zelger B, Steiner H, et al. Solitary giant xanthogranuloma and benign cephalic histiocytosis—variants of juvenile xanthogranuloma. *Br J Dermatol.* 1995;133:598–604.
22. Rodriguez-Jurado R, Duran-McKinster C, Ruiz-Maldonado R. Benign cephalic histiocytosis progressing into juvenile xanthogranuloma: a non-Langerhans cell histiocytosis transforming under the influence of a virus? *Amer J Dermatopathol.* 2000;22:70–74.
23. Sicand E, Pfannes L, Chen G, et al. CD34 cells from patients with trisomy 8 myelodysplastic syndrome (MDS) express early apoptotic markers but avoid programmed cell death by up-regulation of antiapoptotic proteins. *Blood.* 2007;1009:2399–2405.
24. Seward J, Malone J, Callen J. Generalized eruptive histiocytosis. *J Am Acad Dermatol.* 2004;50:116–120.
25. Wee S, Kim H, Chang S, et al. Generalized eruptive histiocytoma: a pediatric case. *Pediatr Dermatol.* 2000;17(6):453–455.
26. Jih D, Salcedo S, Jaworsky C. Benign cephalic histiocytosis, a case report and review. *J Am Acad Dermatol.* 2002;47:908–913.
27. Altman J, Winkelmann R. Xanthoma disseminatum. *Arch Dermatol.* 1962;86:582–596.
28. Caputo R, Veraldi S, Grimalt R, et al. The various clinical patterns of xanthoma disseminatum. *Dermatology.* 1995;190:19–24.
29. Shabbir M, Lucas J, Lazarchick J, et al. Secondary hemophagocytic syndrome in adults: a case series of 18 patients at a single institution and a review of the literature. Hematol Oncol. DOI: 10.1002/hon.960. Published online August 30 2010.
30. Kolde G, Brocker EB. Multiple skin tumors of indeterminate cells in an adult. *J Am Acad Dermatol.* 1986;15:591–597.
31. Segal G, Mesa M, Fishleder A, et al. Precursor Langerhans cell histiocytosis. *Cancer.* 1992;70:547–553.
32. Ventura F, Pereira T, da Luz Duarte M, et al. Indeterminate cell histiocytosis in association with acute myeloid leukemia. *Dermatol Res Pract.* 2010569345. DOI: 10/02/2010. Published online June 21, 2010.
33. Statham BN, Fairris GM, Cotterill JA. Atypical eruptive histiocytosis–a marker of underlying malignancy? *Br J Dermatol.* 1984;110:103–105.
34. Klemke C, Dippel E, Geilen C, et al. Atypical generalized eruptive histiocytosis associated with acute myelogenous leukemia. *J Am Acad Dermatol.* 2003;49:233–236.
35. Saez-de-Ocariz M, Lopez-Corella E, Duran-McKinster C, et al. Benign cephalic histiocytosis preceding the development of insulin-dependent diabetes mellitus. *Pediatr Dermatol.* 2006;23(1):101–102.
36. Weston W, Travers S, Mierau G, et al. Benign cephalic histiocytosis with diabetes insipidus. *Pediatr Dermatol.* 2000;17(4):296–298.
37. Maize J, Ahmed A, Provost T. Xanthoma disseminatum and multiple myeloma. *Arch Dermatol.* 1974;110:758–761.
38. Hammond R, Mackenzie I. Xanthoma disseminatum, with massive intracranial involvement. *Clin Neuropathol.* 1995;14:314–321.
39. Maloney JR. Xanthoma disseminatum: its otolaryngologic manifestations. *J Laryngol Otology.* 1979;93:201–210.
40. Pulsoni A, Anghel G, Falcucci P, et al. Treatment of sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease): report of a case and literature review. *Am J Hematol.* 2002;69:67–71.